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Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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Stereochemistry at the Benzylic Centre in Hydroxyglycitylanthraquinones

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To cite this Article Johnson, Owen , Jones, Derry W. , Mincher, David J. and Shaw, Gordon(1983) 'Stereochemistry at the Benzylic Centre in Hydroxyglycitylanthraquinones', *Nucleosides, Nucleotides and Nucleic Acids*, 2: 4, 367 — 372

To link to this Article: DOI: 10.1080/07328318308078870

URL: <http://dx.doi.org/10.1080/07328318308078870>

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STEREOCHEMISTRY AT THE BENZYLIC CENTRE IN HYDROXYGLYCITYLANTHRAQUINONES

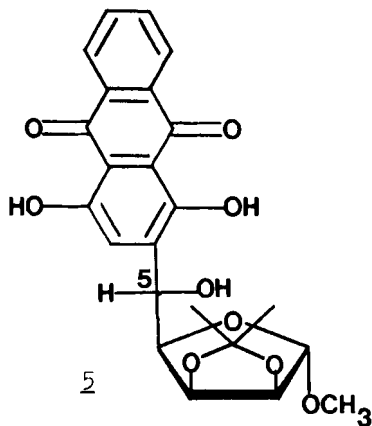
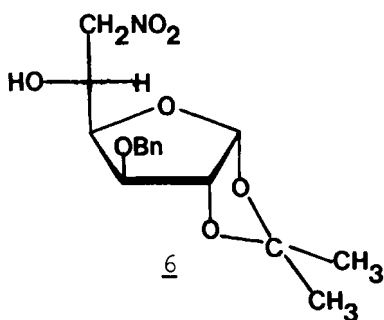
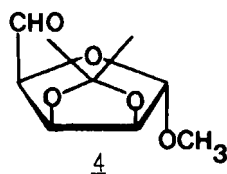
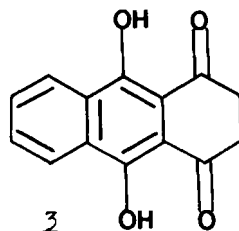
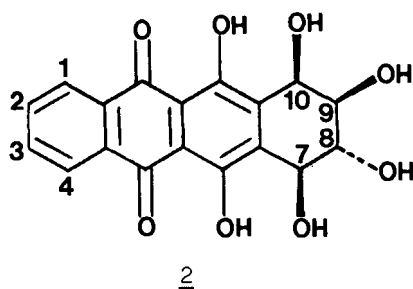
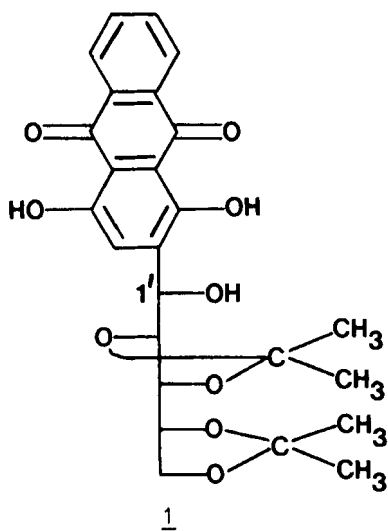
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Abstract. For two anthracyclinone precursors, 1,4-dihydroxy-2-(1-hydroxy-2,3:4,5-di-O-isopropylidene-D-arabinityl)-9,10-anthraquinone (1) and methyl 2,3-O-isopropylidene-5-(2-quinizarinyl)- α -D-lyxofuranoside (5) prepared by a modification of the Marschalk reaction, single-crystal X-ray analyses indicate that the configurations are both S at the new chiral centres C-1' and C-5.

A recently described modification^{1,2} of the Marschalk reaction using a carbohydrate as an aldehyde and chiral template source has led to stereospecific syntheses of hydroxyglycitylquinizarins which are readily convertible to anthracyclinones. The latter constitute the aglycone moiety of the anthracycline antibiotics which include the antitumour drug adriamycin. In particular, 1,4-dihydroxy-2-(1-hydroxy-2,3:4,5-di-O-isopropylidene-D-arabinityl)-9,10-anthraquinone (1), a key intermediate in the synthesis of the novel tetrasubstituted (in ring A) anthracyclinone (2), was produced exclusively as a single diastereoisomer (established by ¹H n.m.r. spectroscopy) by the reaction of an anion derived from leuco-quinizarin (3) with aldehyde 2,3:4,5-di-O-isopropylidene-D-arabinose.^{1,2}



While a normal X-ray analysis of an enantiomorphic structure does not distinguish which of the two possible enantiomeric forms is present, the persistence of the D sugar in (1) can be clearly assumed. Compound (1) crystallizes with two molecules in a monoclinic unit cell $18.74 \times 8.26 \times 7.26 \text{ \AA}$, $\beta = 95.4^\circ$, with space group $P2_1$; its structure has been

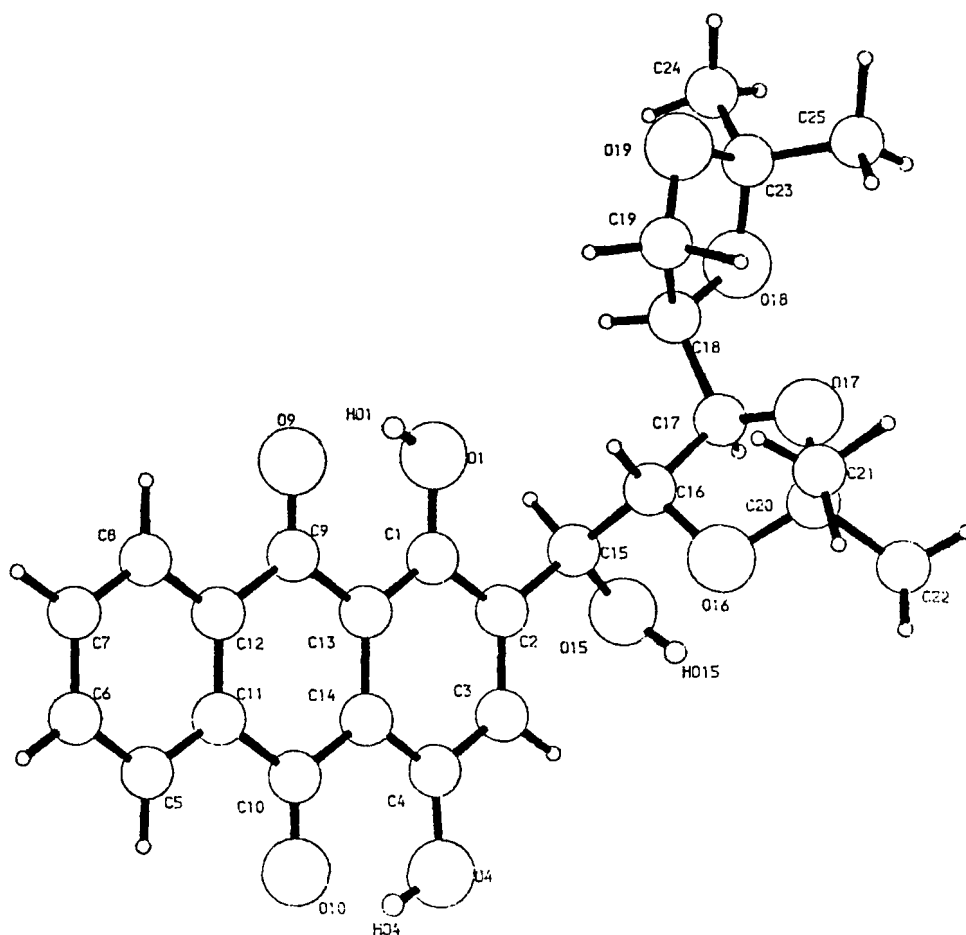


FIG. 1: Projection of molecular structure of 1,4-dihydroxy-2-(1-hydroxy-2,3:4,5-di-O-isopropylidene-D-arabinityl)-9,10-anthraquinone (1)

refined to an R-value of 0.027 over 1604 independent reflections collected from an Enraf Nonius CAD-4F diffractometer. The crystal-structure analysis of (1) indicates that the stereochemistry at the benzylic C-1' chiral carbon-atom (crystallographically labelled C-15 in FIG. 1) is in the S configuration; this corresponds to the predominant diastereoisomer predicted by the application of an extension of Cram's Rule of asymmetric induction³ (derived from a theoretical treatment of carbonyl reduction by organometallic-hydride transfer reagents). The observation is consistent with the D-glucitol configuration established⁵ for the single 1-C-phenyl-D-pentitol diastereoisomer isolated⁴ when aldehyde 2,3:4,5-di-O-isopropylidene-D-arabinose is treated with phenyl magnesium halide.

The modest inhibitory activity against murine leukaemia L1210 cell growth shown by (2)² is relatively promising among anthracycline aglycones since such activity is generally associated with intact anthracyclinone glycosides. Within ring A of (2), the configuration of the hydroxyl groups is known to influence biological activity and the tetra substitution present in (2) may be valuable in the design of new anti-tumour agents. From the results of the X-ray analysis of (1) it can be concluded that the 7,8-trans diol group in (2) is introduced into ring A during the initial condensation rather than in the final cyclisation.

It was of special interest to confirm both the generality of the Marschalk reaction and the tendency for a single specific diastereoisomer to form as at C-1' in compound (1). Accordingly, we have examined other suitable aldehydo carbohydrates including the readily available methyl 2,3-O-isopropylidene- α -D-lyxo-pentodialdo-1,4-furanoside (4) which with leuco-quinizarin (3) produced methyl 2,3-O-isopropylidene-5(S)-(2-quinizarinyl)- α -D-lyxofuranoside (5) [M^+ 442 (M^+); ν_{\max} 1380 cm^{-1} (CMe_2); δ 3.18 (OCH_3); m.p. 176°C] exclusively as a single diastereoisomer in a manner analogous to the preparation of (1). Compound (5) crystallizes with six molecules in a trigonal cell, $a = b = 10.65$, $c = 31.98$ Å, space group $P 3_1 12$. The structure (FIG. 2) was refined to $R = 0.029$ over 2303 independent reflections collected on an Enraf Nonius CAD-4F diffractometer. Again, since the D-lyxose sugar is assured, the X-ray crystal-structure analysis of (5) shows that the new chiral centre C-5 (crystallographically labelled C-19 in FIG. 2) also has the S configuration which corresponds to the preponderant isomer predicted by Cram's Rule.

In general, for addition of Grignard reagents to the aldehydo group in pentodialdo-1,4-furanose derivatives of type (4), the formation of a planar-ring complex involving coordination between the magnesium, carbonyl- and ring-oxygen atoms appears to direct the course of the addition in accord with Cram's Rule.^{6,7} However, in our example, where the rotameric orientation of the carbonyl group in (4) is not constrained by such complexing, Cram's Rule has limited predictive value. Indeed, in a closely analogous reaction involving the addition of the methanenitronate ion to 1,2-O-isopropylidene-3-O-methyl- α -D-xylo-pentodialdo-1,4-furanose, the preponderant isomer (6) (formed in a 2:1 ratio of the two possible diastereoisomers) possesses the D-glucosyl

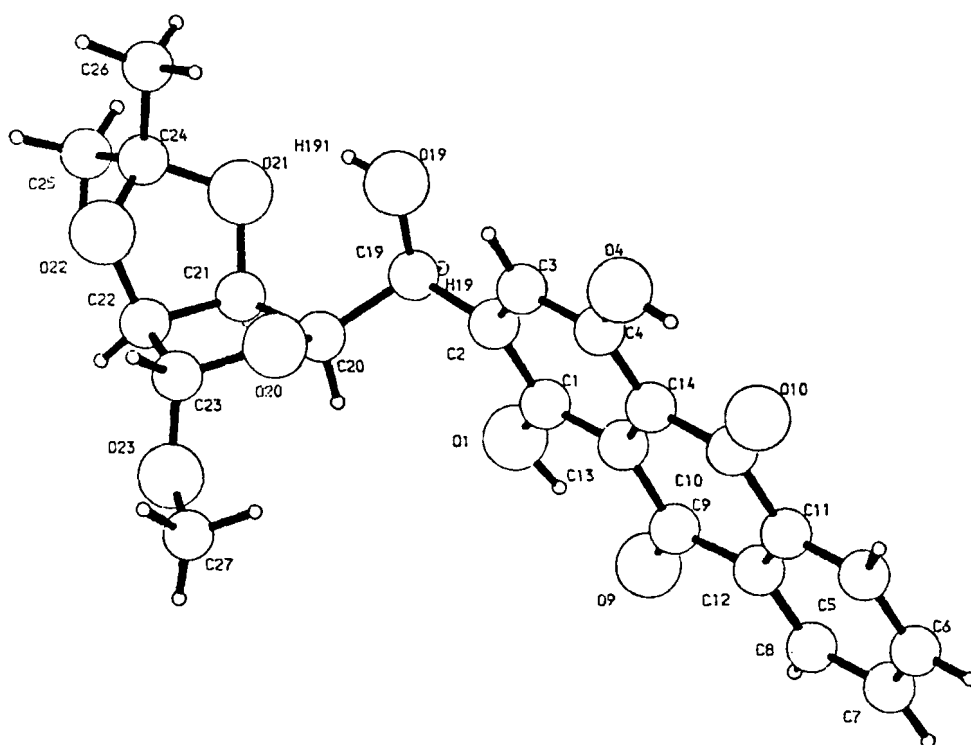


FIG. 2: Projection of molecular structure of methyl 2,3-O-isopropylidene-5-(2-quinizarinyl)- α -D-lyxofuranoside (5).

configuration; this is the less favoured isomer according to Cram's Rule⁸ and it is perhaps therefore surprising that in both our examples, products more analogous to (6) were not produced. Further crystallographic details about the structures of (1) and (5) will be published elsewhere.

ACKNOWLEDGEMENT

We thank the Yorkshire Cancer Research Campaign for research grants (to O.J. and D.J.M.). We are grateful to Dr. D.L. Hughes and Professor M.R. Truter (Rothamstead) and Professor A.C.T. North and Dr. B. Sheldrick (Biophysics, Leeds University) for access to diffractometers.

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Received June 6, 1983